Antibiotic-Resistance Genes in *E. coli* strains in GCC Countries: A Meta-Analysis

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Abstract

Background: Antimicrobial resistance (AMR) in *Escherichia coli* is an alarming issue worldwide, including in the Gulf Cooperation Council (GCC) countries, yet the prevailing gene patterns have not recently been reviewed. This study was conducted to determine and report on the dominant *E. coli* antimicrobial resistant gene patterns in GCC countries.

Method: A scoping review identified the predominant AMR genes in GCC countries: CTX M, TEM, SHV, NDM, OXA, and VIM genes. For the systematic review, two authors independently searched Scopus, PubMed, Google Scholar, Science Direct, and Web of Science for interventional, clinical, or observational studies on the chosen AMR-conferring genes in *E. coli* published from GCC countries between January 2013 and June 2019, when the last search was carried out. The search strategy followed the PRISMA guidelines. The risk of bias was assessed using a 6-item standardized checklist. Random-effects modeling was used for all analyses.

Results: A total 32 studies were included in the final synthesis of evidence. Overall, CTX-M (53.8%) was the most prevalent gene in the region followed TEM (40.6%), NDM-1 (28.4%), OXA (24.3%), VIM (8.5%), and SHV (7.8%). Most included studies were from Saudi Arabia: CTX-M was again most common with a prevalence of 46.8% from 5442 isolates.

Conclusion: The risk of bias analysis showed a mean quality score of 4.25 ± 0.75, indicating high-quality in studies included in this meta-analysis. This review found that CTX-M gene is the most common AMR-conferring gene in *E. coli* strains from most GCC countries.

Keywords: Antimicrobial resistance genes, CTX-M, *Escherichia coli*, Gulf Cooperation Council countries, NDM, OXA

INTRODUCTION

Infections caused by multiple antimicrobial-resistant (AMR) bacteria are a major therapeutic challenge in both hospital and community settings.[1] The Middle East region, which includes the Gulf Cooperation Council (GCC) countries, is not immune to this issue.[2] Studies from this region have identified potential clinical risks associated with extended-spectrum beta-lactamase (ESBL)-producing bacteria,[3,4] NDM-1-carrying resistant bacteria, and other multidrug-resistant strains.[5] This

suggests a potential wide prevalence of antimicrobial resistance in this region.

In Saudi Arabia, antimicrobial resistance has been reported in Gram-negative bacteria isolated from both community and hospital settings,[3] including ESBL-producing *Escherichia coli*.[3,6] Bindayna *et al*.[7] reported that 51% of antibiotic-resistant *E. coli* isolates from this country produced both CTX-M and TEM enzymes, while another reported 22% of the resistant isolates containing both metallo-beta-lactamase (MBL) and ESBL.[8] The United Arab Emirates (UAE) has one of the highest rates of ESBL prevalence in the Arabian Gulf region. A study in 2018 reported the presence of bla_{CTX-M} and bla_{TEM} and bla_{SHV} genes among *E. coli* isolates.[9] NDM, OXA-48 and VIM were also found in the Arabian Peninsula in *E. coli*.[10] A study in Kuwait demonstrated a high prevalence rate CTX-M among *E. coli* isolates. It also reported the presence of VIM and NDM-1.[11] Several studies from Oman have reported carbapenem resistance in *E. coli* is facilitated through NDM and OXA-48 carbapenemases.[12,13] The incidence of antibiotic-resistant bacteria is increasing rapidly in humans in Qatar.[14] For this reason, a hospital-based antibiotic-resistant bacteria surveillance system exists in this country to monitor the antimicrobial resistance from both outpatient and in-patient clinics.[14]

The genotype description of AMR determinants in bacteria plays a crucial role in understanding and controlling the drug resistance.[15] However, to the best of the authors' knowledge, no review has analyzed the AMR gene patterns prevailing in GCC countries. In our scoping review, six AMR genes (CTX M, TEM, SHV, NDM, OXA, and VIM genes) were identified to be dominant in the GCC region. Subsequently, this systematic review was conducted to analyze the AMR patterns of these six genes in *E. coli*.

MATERIALS AND METHODS

The present study used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) as a guideline for reporting the findings.[16]

Search strategy

An electronic search was conducted in Scopus, PubMed, Google Scholar, Science Direct, and Web of Science for articles published between January 2013 and June 2019. We conducted a literature search beginning from 2013 because a previous study has analyzed the prevalence of AMR genes in the GCC between 1999 and 2012. The search strategy included relevant keywords: "antimicrobial resistance" OR "antibiotic resistance" OR "drug-resistance" AND "*Enterobacteriaceae*"

OR "*Escherichia coli*" AND "Middle East" OR "Gulf Co-operation Council (GCC)" OR "Saudi Arabia (KSA)" OR "Bahrain" OR "Kuwait" OR "Oman" OR "United Arab Emirates (UAE)" OR "Qatar" AND "resistant genes" OR "Extended-Spectrum Beta-Lactamase (ESBL)" OR "*Metallo beta-lactamase* (MBL)" OR "CTX- M" OR "NDM" OR "OXA" OR "TEM" OR "VIM" OR "SHV".

Inclusion criteria

Interventional, clinical, and observational studies that analyzed the selected six AMR-conferring genes in *E. coli* clinical isolates from the GCC countries, and in which the resistant genes were detected by molecular methods, were included. A language filter was applied to only include articles published in English. The last search was carried out in June 2019.

Exclusion criteria

To eliminate factors that may incur potential quality or methodological issues, studies were excluded from if any of the following criteria were met:

- Studies that were conducted on *E. coli* strains from environmental resources such as food, water, and air
- Studies that reported secondary data
- Studies on other AMR genes not considered for this study
- Studies reporting resistance genes by phenotypic methods
- Case reports, short communications, abstracts, review articles, letters, editorials, and studies not published in English
- Unpublished/non-peer-reviewed data.

Main outcomes and measures

The principal outcome of this review was to report the prevalence of the selected six AMR genes in GCC countries. Two authors (KMB, RMJ) independently carried out a review of titles and abstracts based on the inclusion/exclusion criteria.

Data extraction

Two authors (KMB, HE) performed the initial data extraction in duplicates. Any discrepancies regarding study eligibility were discussed with the other authors to reach a consensus. To standardize the data extraction, the following variables were collected from each study: type of bacterial isolates, country, year, sample size, and type of antibiotic-resistant genes. Extracted data were entered into Microsoft Excel Sheet for analysis.

Statistical analysis and reporting

One author (HJ) performed the data analysis. A series of single-group meta-analyses was performed based on

the sample size and event rate. Random-effects modeling was used for all analyses; therefore, it was assumed that there is not only one true effect size, rather, a distribution of true effect sizes. The authors sought to estimate the mean of this distribution of true effect sizes. Moderator analysis was performed on the variable country and was done using subgroup analyses. All statistical analyses were performed using the Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA).

Tau (τ^2) and I^2 statistics were used to assess the heterogeneity of the solicited studies within and between studies, respectively. Furthermore, the classical measure of heterogeneity is Cochran's Q, which is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Q is distributed as a Chi-square statistic with k (number of studies) minus 1 degree of freedom.

Critical appraisal of studies (quality assessment)

Two reviewers independently assessed the methodological quality of studies using a standardized checklist consisting of the following six items: sample size, sampling technique, standardization of data collection, appropriateness of statistical analyses, quality of reporting results, and generalizability. The appraisal scores ranged from 0 to 6: Scores of 0–2 correspond to low quality, 3 and 4 to medium quality, and 5 and 6 to high quality. The quality score was set for each study by consensus of all the authors after discussion. We used the Newcastle-Ottawa Scale (NOS) as a guide for assessing the quality of nonrandomized studies in meta-analysis.[17]

RESULTS

Search strategy results

The search retrieved a total of 200 studies (42 studies in Scopus, 51 in PubMed, 38 in Science Direct, 24 in Web of Science, and 45 in Google Scholar). Of these, 114 were screened, the full text of 61 articles was assessed for eligibility, and finally, 32 studies were included for the qualitative synthesis [Figure 1].

Baseline characteristics and risk of bias

Study characteristics (i.e., authors, year, country, sample size, type of antibiotic-resistant genes) are summarized in Table 1. Critical appraisal of studies or quality assessment revealed that the mean quality score was 4.25 (±0.75) [Table 1].

Synthesis of evidence

The initial analysis showed the following prevalence pattern of AMR genes in the GCC region. CTX-M (53.8%) appeared to be the most common AMR gene followed by TEM (40.6%), NDM-1 (28.4%), OXA (24.3%), VIM (8.5%), and SHV (7.8%), respectively. The overview of this result and detailed assessment of heterogeneity are presented in Table 2.

Further, the subgroup analysis was conducted based on the country of published studies. Figures 2–7 summarize this subgroup analysis. In Saudi Arabia, the most commonly found gene was CTX-M: its prevalence was 46.8% of 5442 isolates from 23 studies. Similarly, of the 90 isolates from the three studies from Kuwait, the prevalence of CTX-M was 45.5% [Figure 2]. There were very few studies from other GCC countries.

The prevalence of TEM gene in Saudi Arabia was 44.9% (4751 isolates from 19 studies) and 8.6% in Kuwait (86 isolates from 2 studies) [Figure 3]. The NDM gene was studied in 6 studies from Saudi Arabia, and had a mean point prevalence of 20.5% [Figure 4]. Saudi Arabia also reported studies on OXA gene (9 studies, 23.3% prevalence) and VIM gene (2 studies, 7.4%% prevalence) [Figures 5 and 6]. In terms of the SHV gene, 14 studies were from Saudi Arabia (4852 isolates), 3 from Kuwait (90 isolates), and 2 from Qatar (724 isolates) [Figure 7]. The prevalence of the SHV gene in Saudi Arabia, Kuwait, and Qatar was 8.8%, 11.7%, and 0.6%, respectively. Figure 8 demonstrates the presence of the six antimicrobial resistant genes in *E. coli* in each country.

DISCUSSION

Antibiotic-resistant bacteria, which are a serious threat to the treatment of bacterial infections, arise as a result of exposure to antibiotics in clinical and agricultural settings. Among the Gram-negative bacteria, *E. coli* has emerged as a serious health hazard over the past 20 years.[44] Regional monitoring is necessary for controlling the spread of antimicrobial resistance genes in *E. coli*. To our knowledge, our meta-analysis is the first to report the prevalence of the six AMR genes conducted in the GCC region.

The results presented here showed a predominance of CTX-M gene in the GCC countries. Infections with CTX-M-producing bacteria are of huge importance, as increasing rates of ESBL producers result in prescribing carbapenems, in turn resulting in the emergence and spread of untreatable carbapenem resistance.[45] Articles from Saudi Arabia showed a predominance of CTX-M gene types, which were in proportion to the studies published in Kuwait. This consistency between countries could be due to the misuse or overuse of identical class of antibiotics in humans and
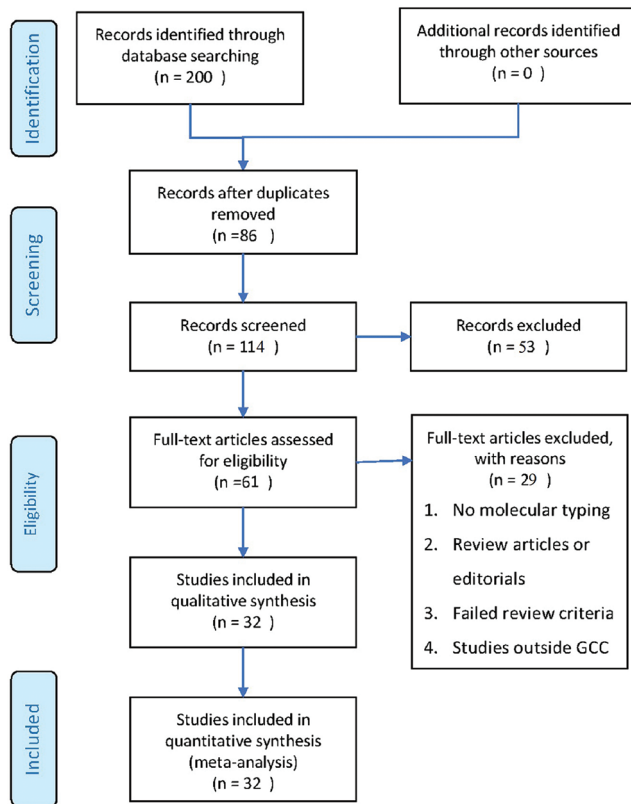
Figure 1: Stages of evaluation of the collected studies

animals, type of population and frequent travel, increased global migration, contamination of the environment and the food chain with human and animal wastes.[46]

In recent years, CTX-M-type ESBLs is reported in Europe, North America and Latin America.[47-49] In fact, the spread of CTX-M gene is prominent worldwide, which is alarming. A study in China reported that CTX-M type accounted for 70% of ESBL-producing E. coli strains in the past 10 years.[50] Studies from Tunisia have reported an increase in the prevalence of CTX-M since 2000 in healthcare settings.[51] A study from south-eastern United States found CTX-M in 68% of the *E. coli* isolates.[52] A study from Southern Chile has reported the presence of CTX-M, TEM and SHV among *E. coli* isolates.[47] Recently, a study from Cuba reported 61.1% of CTX-M among *E. coli* clinical strains.[53] Countries such as India, China, Korea, Japan, and Taiwan have also reported predominance of CTX-M-type ESBLs.[54] Regular global monitoring of the CTX-M gene and the genotypes are important for early intervention in addressing the rise of resistant bacteria.[55]

The present analysis also showed the prevalence of TEM (40.6%), NDM (28.4%), OXA (24.3%), VIM (8.5%), and SHV (7.8%) in the GCC region. In Iran, one study

Table 1: Study characteristics

| Authors	Country	Sample size	CTX-M	TEM	NDM	OXA	VIM	SHV	Quality score
Eltai *et al*., 2018[18]	Qatar	95	65	3				1	5
Elhassan *et al*., 2016[19]	Saudi Arabia	359	57	19				3	5
Abd El Ghany *et al*., 2018[20]	Saudi Arabia	10	9	9	6	5			4
Jamal *et al*., 2013[5]	Kuwait	3	2	1			3	2	4
Jamal *et al*., 2016[21]	Kuwait	4	3		4			0	4
Dashti *et al*., 2014[22]	Kuwait	83	34	2				1	4
Alsultan *et al*., 2013[23]	Saudi Arabia	60	0	44				20	4
Al Sheikh *et al*., 2014[24]	Saudi Arabia	50	3	26				1	4
Zowawi *et al*., 2014[13]	Saudi Arabia	266	7		1	1			5
Al-agamy *et al*., 2014[25]	Saudi Arabia	152	31						5
Hassan *et al*., 2013[26]	Saudi Arabia	139	106	70				33	5
Al-Mijalli, 2016[27]	Saudi Arabia	75	22	15		27		11	4
Marie *et al*., 2013[8]	Saudi Arabia	3358	2698	2465	2338		297	1169	5
Hassan and Abdalhamid 2014[28]	Saudi Arabia	251	81					0	5
Leangapichart *et al*., 2016[29]	Saudi Arabia	10	1	9				1	4
Sonnevend *et al*., 2015[10]	Arabian Peninsula	28			9	9	1		4
Alyamani *et al*., 2017[30]	Saudi Arabia	58	27	22		28		2	4
Abd El Ghany *et al*., 2018[20]	Saudi Arabia	10	6		6	4			3
Alzahrania *et al*., 2016[31]	Saudi Arabia	14	3	14					3
Hassan *et al*., 2014[32]	Saudi Arabia	15	9						3
Mashwal *et al*., 2017[33]	Saudi Arabia	117	10	3				0	5
Soliman *et al*., 2018[34]	Saudi Arabia	46	28	2				3	4
Ahmed *et al*., 2016[35]	Qatar	629	29	13				3	5
Alfaresi *et al*., 2018[9]	UAE	39	39	39			2	15	4
Shahid, 2014[36]	Bahrain	75	70						4
Yasir *et al*., 2018[37]	Saudi Arabia	211	201	177		14		11	5
Alam MZ *et al*., 2016[38]	Saudi Arabia	877							5
Alqasim *et al*., 2018[39]	Saudi Arabia	100	31	4		8	0		5
Leangapichart *et al*., 2016[40]	Saudi Arabia	18	17	5					4
Somily *et al*., 2015[41]	Saudi Arabia	50	48	13				0	4
Ahn *et al*., 2015[42]	UAE	1			0	1			2
AlTamimi *et al*., 2017[43]	Saudi Arabia	26			1	6			4
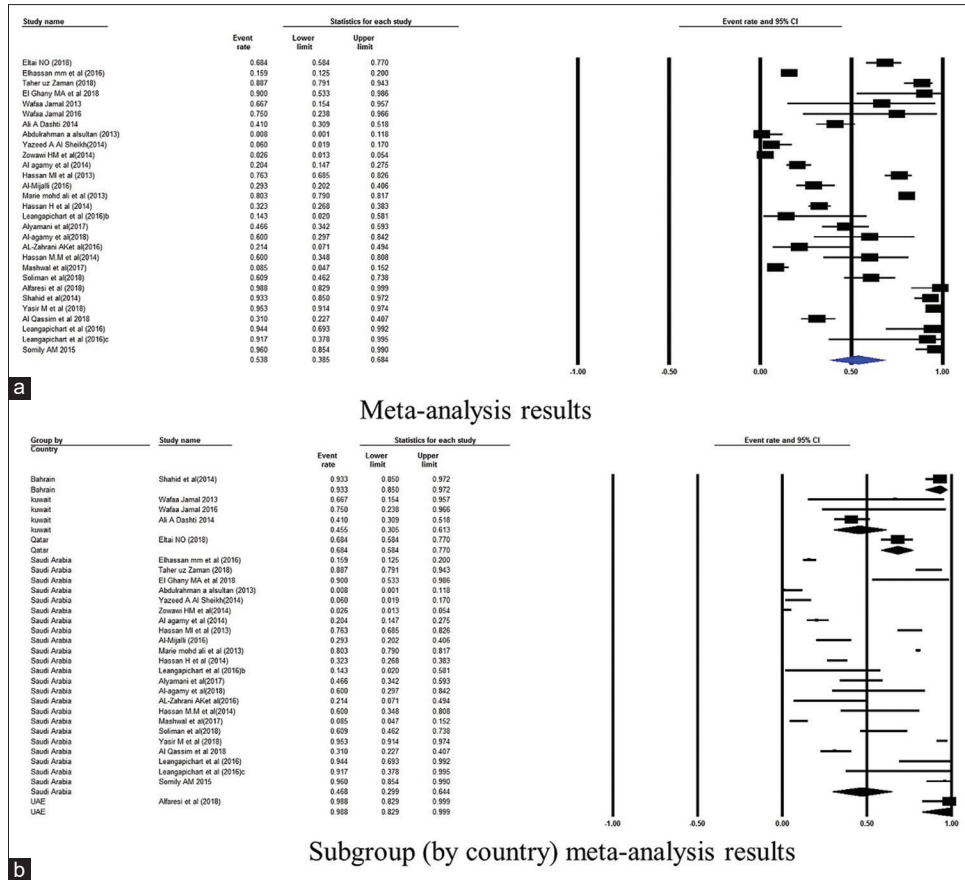
Figure 2: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for CTX-M gene. CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis

Table 2: Prevalence of antimicrobial resistance genes

Parameters	CTX M	TEM	NDM	OXA	VIM	SHV
Number of studies (K)	29	23	8	10	5	20
Number of isolates (n)	6428	5600	3774	856	3454	5705
Proportion (95% CI)	53.8 (38.5-68.4)	40.6 (25.8-57.4)	28.4 (9.6-59)	24.3 (11.3-44.7)	8.5 (2.9-22.6)	7.8 (4.1-14.3)
Q	1262.909	706.709	130.882	147.876	10.866	298.658
Df (Q)	28	22	7	9	4	19
P	0.001	0.001	0.001	0.001	0.028	0.001
I^2	97.783	96.887	94.652	93.914	63.186	93.638
Tau^2	2.483	2.256	2.979	1.988	0.914	1.743

CI: Confidence interval, df: Degree of freedom

reported that the frequency of SHV and TEM was 8.4% and 50%, respectively,[56] while another reported it as 92% and 70%, respectively, from strains isolated from bile specimens.[57] In addition, Kazemian *et al.* reported the presence of CTX-M in 21.5%, TEM in 16.9% and SHV in 16.9% of *E. coli* strains.[58] In India, the frequency of CTX-M among *E. coli* isolates was reported at 57.7%, TEM 30.1%, SHV 10.6%, and NDM-1 18.2%.[59] Recently, a study from Cuba reported 31.7% TEM and 0.7% NDM-1 among *E. coli* clinical strains.[53] A study in Turkey observed TEM and CTX-M in 72.72% and 22.72% of *E. coli* isolates.[60]

In Europe, the prevalence of carbapenem resistance is yet relatively low (0–1.6%). In a recent study by Sepp *et al.*, where 10,780 clinical *E. coli* strains from Northern and Eastern Europe were screened, only one NDM-1-producing *E. coli* was found. The authors also reported that the most commonly observed carbapenemase was bla_{OXA-48}.[61] Another study from Germany also found that the most common carbapenemase was OXA-48, and this has rapidly spread from Europe and the Middle East to every continent.[62] The major reservoir of NDM producers in the Asian continent is China and India, with an abundance of NDM-1 variants.[63] Low prevalence of NDM-1 gene has also been reported from Pakistan and the United Kingdom.[64] However, the spread of these isolates in the community necessitates an urgent call for resistance surveillance and molecular characterization of the resistant genes.[65]
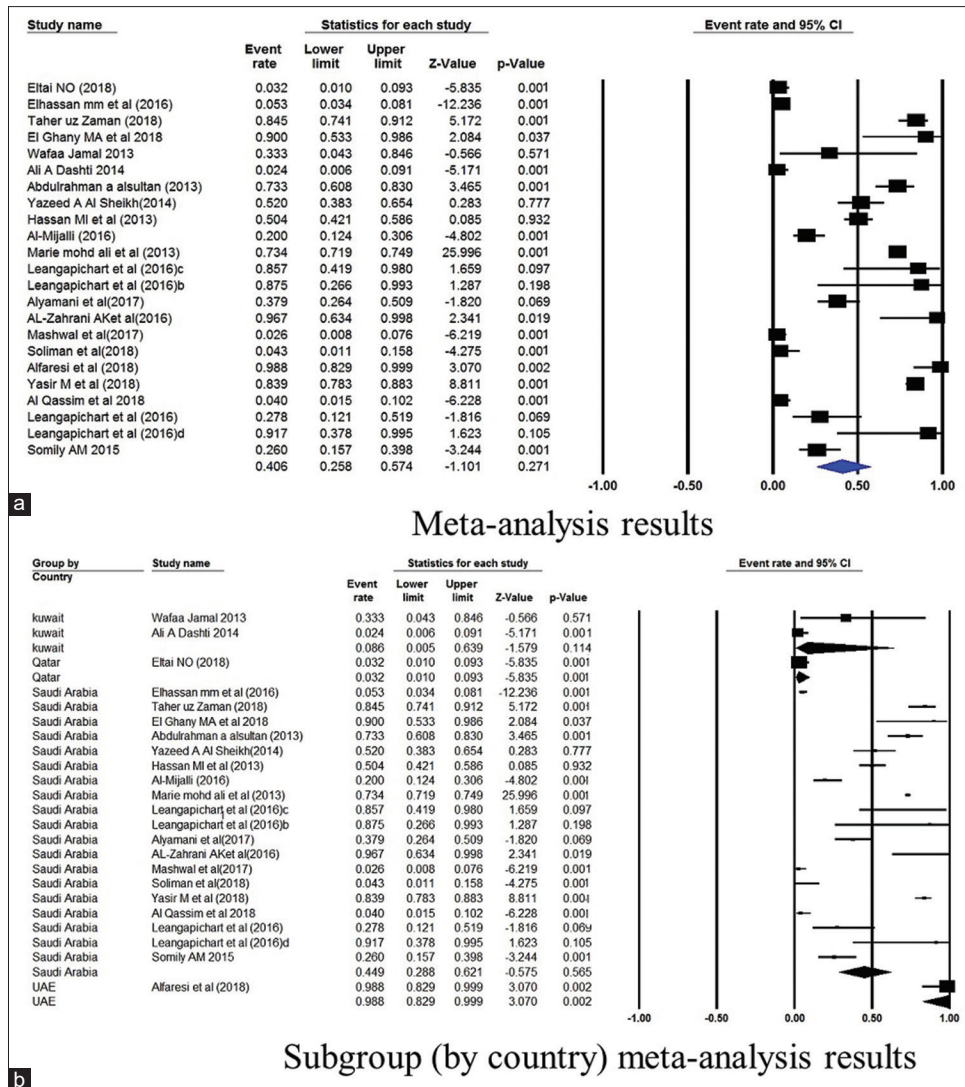
Figure 3: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for TEM gene. CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis

Bell *et al.*[66] observed a strong relationship between antibiotic consumption and resistance in southern European countries. He stated the critical components of a strategy responsible to reduce bacterial resistance are the individual level prescribing and also the public policy addressing the problem at the national and the regional levels. Another factor contributing to the emergence and spread of resistance is self-medication.[67] Antibiotics consumption may not only produce resistance at the individual level but also spread resistance at the community, national, and regional levels.[66] Other factors contributing to antibiotic resistance are the presence of highly susceptible immunocompromised patients (e.g., cancer patients, or transplant recipients), fragile elderly patients, and inappropriate infection control measures in the hospital settings.[68]

The study has a limitation of lack of analysis of all the AMR genes in the GCC countries. Because of the low number of studies identifying resistance mechanisms in various GCC countries, the extent of the AMR resistance is not fully known.

CONCLUSION

This meta-analysis found that CTX-M gene is the most common AMR-conferring gene in *E. coli* strains from most GCC countries, generally followed by TEM, NDM, OXA, VIM, and SHV antimicrobial-resistance genes. These results indicate the need for more stringent and active measures across various platforms to raise awareness, stewardship, and surveillance to prevent and control further multidrug-resistant *E. coli* infections.

Data availability statement
The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.
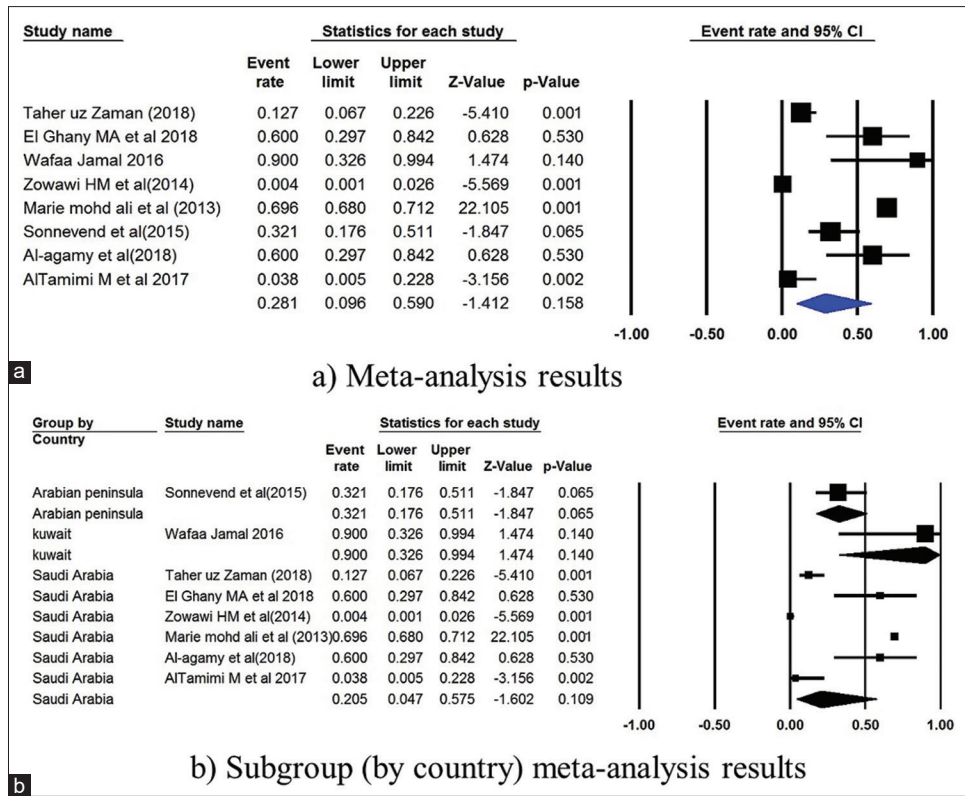
Figure 4: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for NDM gene. CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis
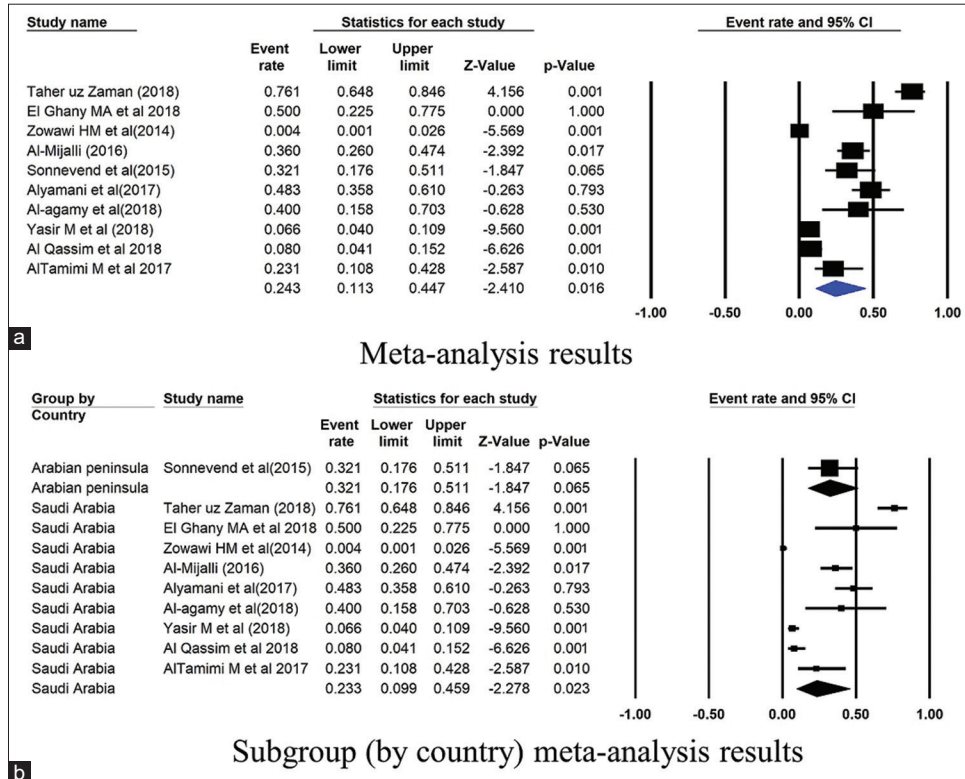

Figure 5: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for OXA gene. CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis

Figure 6: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for VIM gene**.** CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis
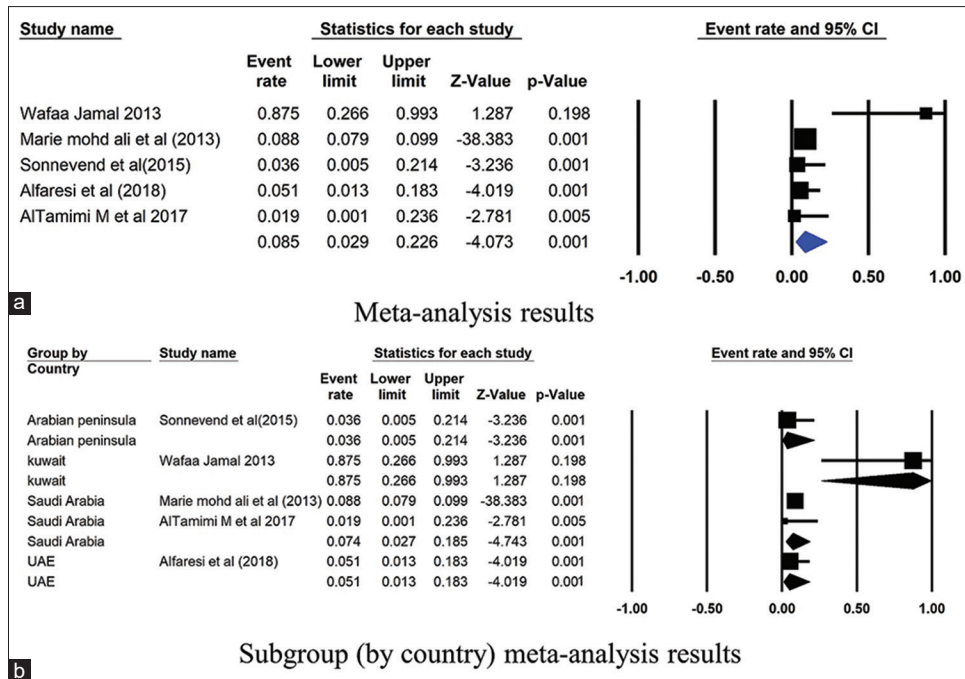

Figure 7: Forest plots showing (a) meta-analysis results (b) subgroup (by country) meta-analysis results for SHV gene**.** CI, confidence interval. Horizontal lines stand for 95% CIs. The size of the squares shows the weight that individual study had in the meta-analysis
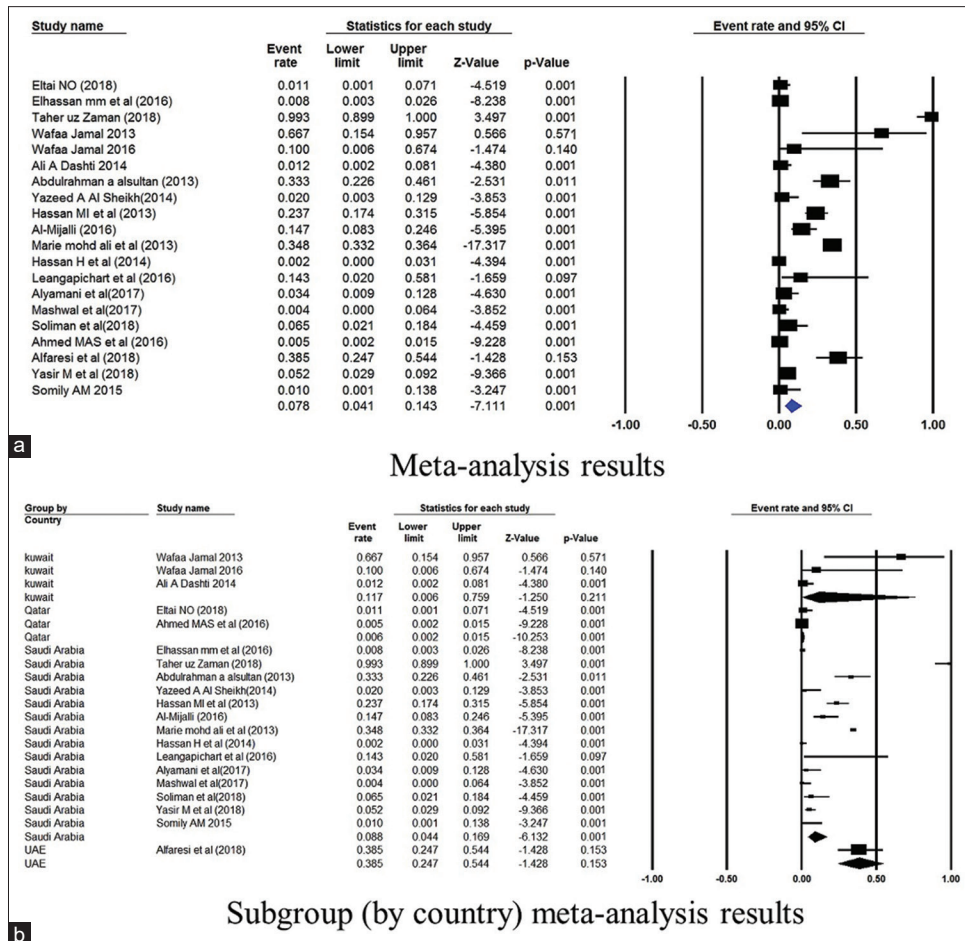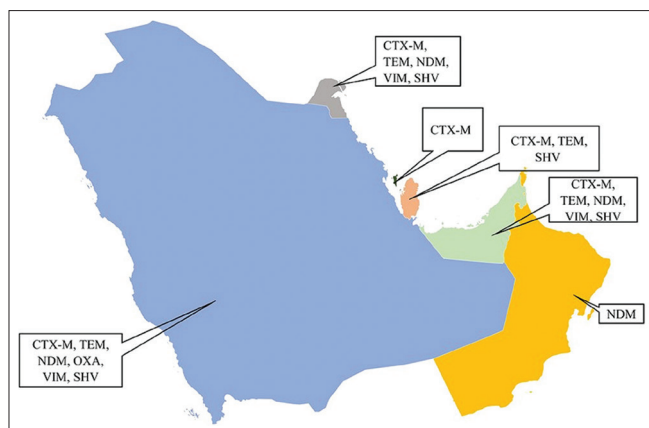
Figure 8: Antimicrobial resistant genes in *E. coli* in various GCC countries

Peer review

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Conflicts of interest

There are no conflicts of interest.

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